ABBOTT

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December 20, 1999

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20857

RE: Draft Guidance for Industry on Average, Population and Individual Approaches to Establishing Bioequivalence
[Docket No. 97D-0433]

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people and serving customers in more than 130 countries.

Overall, we find the guidance document to be a thoughtfully prepared and balanced survey of the issues covering the approaches to establishing bioequivalence. We have a specific remark on the selected sections of the draft guidance as shown below.

1. Page 9: The Draft Guidance states the following:

V. STUDY DESIGN

C. Study Population

" ...giving informed consent. An attempt should be made to enter as heterogeneous a study population as possible, with a reasonable balance of males and females, young and elderly, and subjects of differing racial groups. Restrictions to entry..."

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2. Page 16: The Draft Guidance *also* states:

VII. MISCELLANEOUS ISSUES

Outlier Considerations

2. Subject-by-Formulation Interaction

"A subject-by-formulation interaction could occur when an individual is representative of subjects present in the general population in low numbers, for whom the relative BA of the two products is markedly different than for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population."

Response:

The guidance recommends inclusion of subpopulations according to sex, race and age, but leaves out subpopulations that may have rapid gastrointestinal transit or achlorhydria. While it is true that sex, race and age are much easier to establish, a characteristic like rapid gastrointestinal transit could be much more likely to result in a subject-by-formulation interaction (SFI).

With a replicate study design and individual bioequivalence method of analysis it is theoretically possible to identify SFI. However, it will not be easy to identify SFI in a typical bioequivalence (BE) study conducted in 24-36 healthy subjects. It is highly unlikely that adequate representation of all subgroups could be achieved in a study of this size. A BE study in 24-36 subjects will have little statistical power to detect a SFI, and will not indicate that SFI are absent from the general population. The results of such a study may even give a false sense of security regarding SFIs. In contrast, a BE study designed to include such subgroups and powered to detect SFI will require a very large number of subjects and could be very expensive.

SFI can be better identified during post marketing surveillance or in studies conducted in large number of patients, but the replicate BE study powered using variability estimates from healthy subjects may not be adequate in size to include enough subjects from any subgroup to detect clinically-relevant SFIs in the general population.

3. Concluding Remarks

We recommend that the final promulgation and implementation of any proposed guidance should be undertaken after an open discussion between industry, the FDA and academia. The rationale for this comment is due to the scope and potential implications relating to the design and cost of clinical trials. Finally, public seminars covering a final draft of this guidance will serve to clarify regulatory expectations and interpretations.

Thank you for the opportunity to comment.

Yours truly,

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cc: Mei-Ling Chen, (HFD-870)

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